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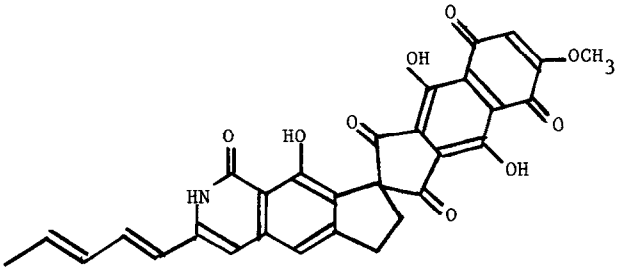
SYNTHESIS OF THE SPIROCYCLIC CENTER OF FREDERICAMYCIN A BY PHENOXY-ENOXY RADICAL COUPLING

Andrew S. Kende*, Frank H. Ebetino
and Toshiharu Ohta[1]
Department of Chemistry, University of Rochester
Rochester, NY 14627

Summary: Ferricyanide oxidation of the dianions of phenolic β-diketones 2 effects intramolecular phenoxy-enoxy radical coupling to form spiro systems derived from C-C bond formation para or ortho to the phenolic oxygen.

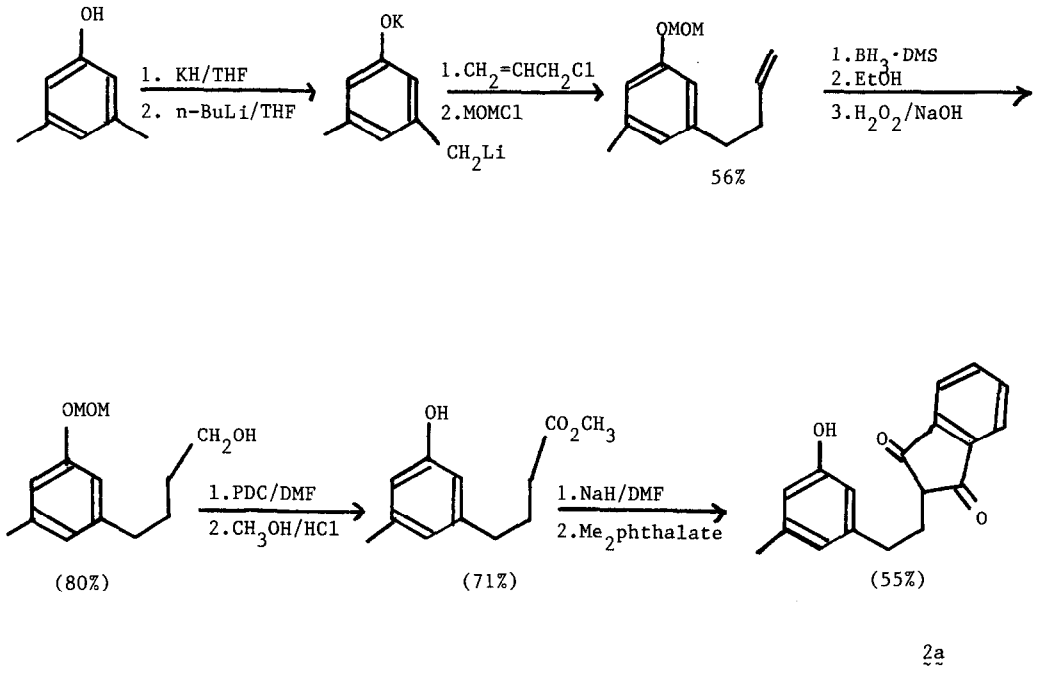
The intramolecular coupling of two phenoxy radicals to form a new carbon-carbon bond has been long recognized as a major biosynthetic and important synthetic route to certain alkaloids and polyketide substances.[2] We are unaware of the related coupling between a phenoxy radical and an enoxy radical in natural products synthesis.[3] We now report this possibly biomimetic model for the facile construction of the spirocyclic diketone center of the unique antitumor antibiotic fredericamycin A (1).[4]



1

The phenolic β-diketone 2a[5] was prepared in five synthetic operations from 3,5-dimethylphenol in 18% overall yield as in Scheme 1. The dianion of 3,5-dimethylphenol (KH in THF at 0°C, then 1.2 eqts of n-BuLi in hexane at 0°C, 20 m)[6] was reacted at -78°C with allyl chloride, followed in 3 hours by quenching at 0°C with methyl chloromethyl ether to give O-methoxymethyl-3-(4'-butenyl)-5-methylphenol. Reaction with excess $BH_3 \cdot SMe_2$ (0°C, 4 h) then with alkaline H_2O_2 gave the corresponding alcohol which was directly oxidized (PDC, 3.5 eqt, DMF, 0°C, 18 h) to the arylbutyric acid, mp 54-56°C. The corresponding ester was condensed with dimethyl phthalate[7] to yield the diketone 2a as colorless flakes from methanol, mp 123-124°C.[8]

Scheme 1

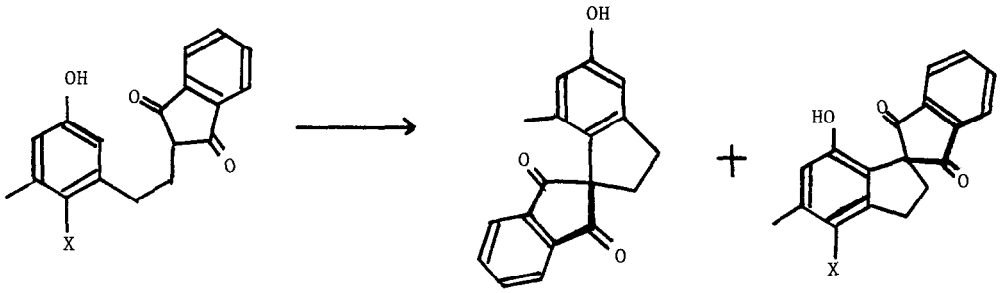


2a

Treatment of 2a at 0°C in 0.5 M Na_2CO_3 with 6 eqts of 0.5 M $K_3Fe(CN)$[2,9] and workup after 10 min using citric acid gave in 67% yield the pale yellow para-coupling product 3, mp 253-254°C,[10] and 8% of the desired colorless ortho-coupling product 4a, mp 221-113°C.[11] Differentiation between these regioisomers was facilitated by the 0.5 ppm upfield shift of the Ar-CH_3 signal of para product 3 (δ 1.73) relative to either 2a (δ 2.23) or 4a (δ 2.26) as a result of shielding in 3 by the newly proximate, perpendicular aryl ring (cf. Scheme 2).

Attempts to modify the cyclization regiochemistry by the use of higher pH or other oxidants[2b] (e.g., MnO_2, $FeCl_3$, VOF_3-TFA, $VOCl_3$, $Tl(CF_3CO_2)_2$, $CuCl_2$[3]), failed to produce either cyclization product. We therefore reacted our phenolic arylbutyrate ester with ICl in acetic acid (1.0 eqt, 8°C, 30 m) to give 93% of the corresponding p-iodo ester.[12] This was condensed with dimethyl phthalate to give 45% of iodo diketone 2b, mp 159-161°C (dec).[13] Oxidative coupling as described produced 46% of a single spirodiketone, mp 157-160°C (dec), assigned structure 4b because of the close correspondence of its spectra [IR($CDCl_3$): 1740, 1704 cm^{-1}; ^{1}H-NMR($CDCl_3$): 2.36(3H,s), 2.47(2H,t,J=7.6 Hz), 3.27(2H,t,J=7.6 Hz), 6.43(1H,s), 7.88(2H,m), 8.02(2H,m)] with that of the minor product 4a from the earlier cyclization

Scheme 2



2a (X=H)
2b (X=I)

3

4a (X=H)
4b (X=I)

Deiodination of 4b could not be selectively carried out using H_2-catalyst systems because of competing reduction of the 1,3-dione unit. Although 4b was inert to Bu_3SnH under the usual conditions,[14] selective reduction of iodine was achieved photochemically.[15] Thus irradiation of 4b in isopropanol containing excess NaOAc, using a 140 W. Hanovia UV source in a Pyrex reaction vessel at 60-70°C for 10 hours, gave 59% of the desired ortho-coupled spirodiketone 4a accompanied by 25% of recovered 4b.

These preliminary studies suggest that such mild phenoxy-enoxy coupling could serve to construct the spirodiketone center in a total synthesis of fredericamycin A from appropriate precursors.[16]

References and Footnotes

1. On leave from Faculty of Pharmaceutical Sciences, University of Tokyo.
2. (a) "Oxidative Coupling of Phenols," Eds. Battersby, A. R.; Taylor, W. I.; Dekker, New York, 1967 (b) Dhingra, O. P. in "Oxidations in Organic Chemistry," Ed. Trahanovsky, W. S.; Part D, Ch. IV, Academic Press, New York 1982, and references therein.
3. Couplings of enoxy radicals are reported: (a) Ito, Y.; Konoike, T.; Saegusa, T. J. Am. Chem. Soc. 1975, 97, 649 (b) Frazier, R. H., Jr.; Harlow, R. L. J. Org. Chem. 1980, 45, 5408, and references therein.
4. For structure, see Misra, R.; Pandey, R. C.; Silverton, J. V. J. Am. Chem. Soc. 1982, 104, 4478. A recent synthetic approach to the spirocyclic dione system of fredericamycin is by Rao, A. V. R.; Reddy, D. R.; Deshpande, V. H. J. Chem. Soc., Chem. Commun. 1984, 1119.

5. All compounds for which mp are given gave satisfactory C, H, or mass spectrometric analyses.

6. We are indebted to Dr. Lee Latimer (Eastman Kodak Co.) for providing these reaction conditions from his laboratories.

7. Koelsch, C. F.; Byers, D. J. J. Am. Chem. Soc. 1940, 62, 560.

8. 2a: ^{1}H-NMR($CDCl_3$,δ): 2.23 (3H,s), 2.24(2H,dt,J=6.0, 7.8), 2.76(2H,t,J=7.8), 3.04(1H,t, J=6.0), 5.28(1H,bs), 6.50(1H,s), 6.53(1H,s), 6.58(1H,s), 7.86(2H,m), 7.98(2H,m).

9. Eg, Day, A. C. J. Chem. Soc. 1964, 3001.

10. 3: IR($CHCl_3$,ν): 1740, 1702, 1595 cm^{-1}; UV(CH_3OH, λ, log ε): 382(2.33), 302(3.21), 278 (3.61), 248(4.23); ^{1}H-NMR($CDCl_3$,δ): 1.73(3H,s), 2.46(2H,t,J=7.5), 3.19(2H,t,J=7.5), 4.98 (1H,bs), 6.39(1H,s), 6.63(1H,s), 7.93(2H,m), 8.08(2H,m); ^{13}C NMR(DMSO-d_6,δ): 19.9, 32.1, 36.8, 66.0, 109.6, 115.8, 123.8, 130.7, 134.4, 137.2, 141.5, 148.8, 158.5, 203.0. In the Rao diketone the spiro and carbonyl carbons in the ^{13}C NMR are at δ 68.2 and 201.5, respectively.[4] The UV of 3 was unchanged on rechromatography.

11. 4a: IR($CHCl_3$,ν): 1740, 1700, 1595 cm^{-1}; UV(CH_3OH, λ, log ε): 275(3.58), 246(4.06); ^{1}H-NMR($CDCl_3$,δ): 2.26(3H,s), 2.46(2H,t,J=7.8), 3.22(2H,t,J=7.8), 4.79(1H,bs), 6.27(1H,s), 6.74(1H,s), 7.87(2H,m), 8.02(wH,m). In fredericamycin A the two adjacent methylenes are at δ 2.55 (t,J=6) and 3.22(t,J=6).[4]

12. Papa, D.; Ginsberg, H. F.; Lederman, I.; DeCamp, V. J. Am. Chem. Soc. 1953, 75, 1107.

13. 2b: ^{1}H-NMR($CDCl_3$,δ): 2.24(2H,q,J=8.0), 2.42(3H,s), 2.98(2H,t,J=8.0), 3.08(1H,t,J=8.0), 6.66(2H,s), 7.87(2H,m), 8.01(2H,m).

14. Brown, H. C.; Liu, K.-T. J. Am. Chem. Soc. 1970, 92, 3502 and references therein.

15. Cf. Friedman, P., Abst. 148th American Chemical Society Meeting (Chicago, 1964), Orgn. p. 275.

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